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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,497	02/17/2000	DAVID J. FITZGERALD	015280-317100US	4036

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	PAPER NUMBER
1642	26

DATE MAILED: 08/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/381,497	FITZGERALD	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-11,13,14,16,17,22-26 and 29-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-11,13,14,16,17,22-26 and 29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1 and 11 have been amended.

Claims 5, 12 and 27 has been canceled.

Claims 1-4, 7-11, 13-14, 16-17, 22-26, 29-32 are under examination.

2. The text of those sections of title 35, USC Code not included on the Office Action can be found in a prior Office Action.

3. The following Office Action contains a NEW GROUND of rejection.

Rejections Withdrawn

4. The rejection of claims 1-4, 7-11, 13-14, 16-17, 22-26, 29-32 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of the amendments to the claims.

5. The rejection of claims 1-4, 7-11, 13-14, 16-17, 22-26, 29-32 under 35 U.S.C. 103(a) as being unpatentable over Ghetie et al (Cancer Res. 51:5876-5880, 1991) and further in view of Shen et al (Int. J. Cancer 42:792-797, 1988) and Reiter et al (Biochemistry 33:5451-5459, 1994) and Kuan et al (Biochemistry 35:2872-2877, 1996, Abstract published 2/1/96) and Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989) is withdrawn in view of the new ground of rejection.

Response to Arguments

6. The rejection of claims 11, 13-14, 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

The response filed 7/14/03 has been carefully considured but is deemed not to be persuasive. The response did not apparently address this rejection. the response on page 6 of the response only appears to address the 112 first rejection for immunoconjugates that are 95% identity to SEQ ID NO:2 or 4 and 90% or greater binding affinity. The response does not address the rejection of Claim 11 which still recite the limitation of "immunoconjugate comprising a sequence encoding for a toxin peptide and an antibody that binds to an RFB4 disulfide-stabilized Fv (dsFv)". The specification does not disclose any antibody immunoconjugate that binds to the RFB4 dsFv. Applicant is required to provide specific support in the application as originally filed for the limitation or remove the limitation from the claim.

The following is a NEW GROUND of rejection

Claim Rejections - 35 USC § 103

7. Claims 1-4, 7-11, 13-14, 16-17, 22-26, 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghetie et al (Cancer Res. 51:5876-5880, 1991) and further in view of Shen et al (Int. J. Cancer 42:792-797, 1988) and Reiter et al (Biochemistry 33:5451-5459, 1994) and Kuan et al (Biochemistry 35:2872-2877, 1996, Abstract published 2/1/96) and Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989), Cabilly et al (U.S Patent 4816567, issued 3/89), Boss et al (U.S Patent 4816397, issued 3/89), Robinson et al (U.S. Patent 5618920, filed 4/94), Ward et al (Nature 341:544-546, 1989), and Huston et al (U.S. Patent 5258498, issued 11/93).

The claims recite a recombinant immunoconjugate comprising a therapeutic or detectable label covalently linked to a recombinant RFB4 disulfide stabilized FV having a heavy chain of SEQ ID NO:2 which has a cysteine at position 44 and a light chain of SEQ ID NO:4 with a cyteine at position 100, wherein the VH is bonded to the amino terminus of PE and the VH and VL are bonded through a linker of SEQ ID NO:5 or cysteine-cysteine disulfide bond, an expression cassette comprising such, a host cell, a method of inhibiting the growth of malignant B-cells in a rodent.

Ghetie et al teach the RFB4 anti-CD22 antibody conjugated to ricin A chain and inhibition of growth of B-cell lymphomas in mice. The claimed VH and VL are from the RFB$ antibody with the substitutions indicated. Ghetie et al does not teach the hybridoma for RFB4, an anti-CD22 antibody with a VH with a cysteine at position 44 or a VL with a cysteine at position 100 conjugated to a cytotoxic fragment of PE wherein the VH is linked to the PE at the amino terminus, and the VH and VL are linked through a peptide linker that has SEQ ID NO:5 or a disulfide bond, or an expression cassette

comprising such or a method of inhibiting the growth of malignant B-cells with a anti-CD22 antibody PE conjugate. These deficiencies are made up for in the teachings of Kuan et al, Reiter et al, Shen et al, and Orandi et al, Cabilly et al, Boss et al, Robinson et al, and Ward et al and Huston et al.

Shen et al teach the hybridoma which produces the RFB4 antibody (see Antibodies under Material and Methods on page 792) and the RFB4 antibody can be a Fab' and the RFB4 antibody is the choice for preparing Fab' immunotoxins (see abstract).

Reiter et al teach recombinant immunotoxins comprising disulfide stabilization with a cysteine at position 44 in the VH and a cysteine at position 100 in the VL. The antibody is conjugated to a toxin of PE38. Reiter et al also teach the VH is linked to the amino terminus of PE38 (see Figure 2). Reiter et al teach a general method for producing disulfide stabilized immunotoxins (see page 5453, Results).

Kuan et al teach a disulfide stabilized Fv directed to a cancer antigen. Kuan et al teach the VH is linked to the amino terminus of PE38 and the VH and VL are linked through a sequence that has SEQ ID NO:5 and the VH and VL are linked through a disulfide bond and expression cassettes and host cells comprising such and methods of producing such and the method produces the dsFV immunotoxins more stable.

Orlandi et al teach a general method for obtaining the VH and the VL genes and the amino acid sequence of an antibody by PCR from the hybridoma cell. Orlandi also teaches primers and the use of said primers to clone DNA encoding murine variable

heavy regions (see page 3833 and 3834) and the method obtained the sequences for five of the hybridomas for which it was applied.

Robinson et al (see columns 12-22) and Ward et al (see entire document) teach Fv derived from a known antibody. Robinson et al teach Fv, determination of nucleic acids encoding VH and VL of any known antibody and use of said VH and VL to produce FV (see column 1-45, and columns 12-22). Robinson et al teach that "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Ward et al teach vectors for producing FV.

Both Cabilly et al and Boss et al disclose methods for the determination of nucleic acids encoding VH and VL of any known antibody.

Huston et al teach that the sequence of the VH and VL of a known antibody can be determined by amino acid sequencing and "The 5' end portion of the mRNA can be used to produce the cDNA for subsequent sequencing or the amino acid sequence of the hypervariable and flanking framework regions can be determined by amino acid sequencing of the V regions of the H and L chains. Such sequence analysis is now conducted routinely".

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody RFB4 and obtain the DNA and protein sequence of the VH and the VL from the RFB4 hybridoma as taught by Shen et al by the method of Orlandi et al, Cabilly et al, Boss et al, Robinson et al, Ward et al and

Huston et al, and use the method of inhibiting malignant B-cells as taught by Ghetie et al and use the method of Reiter et al and Kuan et al to produce a disulfide stabilized anti-CD22 antibody conjugate of RFB4.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody RFB4 and obtain the DNA and protein sequence of the VH and the VL from the RFB4 hybridoma as taught by Shen et al by the method of Orlandi et al, Cabilly et al, Boss et al, Robinson et al, and Ward et al and Huston et al and the method of inhibiting malignant B-cells as taught by Ghetie et al and use the method of Reiter et al and Kuan et al to produce a disulfide stabilized anti-CD22 antibody conjugate of RFB4 because Ghetie et al teach that the RFB4 conjugates inhibited protein synthesis and when administered to mice with tumors, extended the mean survival time (see abstract). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody RFB4 and obtain the DNA and protein sequence of the VH and the VL from the RFB4 hybridoma as taught by Shen et al by the method of Orlandi et al ,Cabilly et al, Boss et al, Robinson et al, and Ward et al and Huston et al and the method of inhibiting malignant B-cells as taught by Ghetie et al and use the method of Reiter et al and Kuan et al to produce a disulfide stabilized anti-CD22 antibody conjugate because Reiter et al teach a general method of stabilizing Fv's with insertion of cysteine residues in the conserved framework residues (see page 5453, Results) and "Neither molecular modeling nor knowledge of the structures of these Fv's was necessary to identify these positions" (see page 5453) and "disulfide-stabilized Fv's

could be used not only to generate immunotoxins but also for all of the diagnostic and therapeutic uses proposed for single-chain antibodies or antigen binding proteins" (see page 5458). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody RFB4 and obtain the DNA and protein sequence of the VH and the VL from the RFB4 hybridoma as taught by Shen et al by the method of Orlandi et al Cabilly et al, Boss et al, Robinson et al, and Ward et al and Huston et al and the method of inhibiting malignant B-cells as taught by Ghetie et al and use the method of Reiter et al and Kuan et al to produce a disulfide stabilized anti-CD22 antibody conjugate because Kuan et al teach immunotoxins comprising a disulfide stabilized VH and VL wherein the VH is linked to the amino terminus of the PE38 and "We have compared the stability of three different single-chain and dsFv inmmunotoxins, and in all three cases the dsFv immunotoxins were more stable (see page 2872). Moreover, it would have been obvious to one of skilled in the art at the time the claimed invention was made to use a linker which has SEQ ID NO:5 to link the VH and the VL domains as was commonly performed.

Although the references do not teach the amino acid sequences of SEQ ID NO:2 and 4 for the VH and VL of the anti-CD22 RFB4 antibody, the references cited in this rejection teach FV, nucleic acids encoding VH and VL and the methods of making FV based on the nucleic acid sequence of any known antibody VH and VL , and methods of determining the nucleic acid sequence of any known antibody VH and VL. All Fv are structurally similar in that they contain similar numbers of amino acids organized in a similar fusion (e.g. they contain a VH and VL wherein the VH and VL contain framework

and variable region amino acids). Thus it would not have been undue experimentation to obtain SEQ ISD NO:2 and 4 because the art recognizes that hundreds, if not thousands of antibody molecule VH and VL regions have been cloned and sequenced. As taught by Orlandi et al it was routine to obtain the VH and the VL genes from PCR primers from the hybridoma of an antibody and "our primers might amplify most immunoglobulin mRNA of the mouse repertoire" (see page 3836, right column) and "the teachings should lead to the cloning of antigen-binding specificities directly from immunoglobulin genes" (see abstract, last sentence). Cabilly et al teach that regarding VH and VL nucleic acid sequences that, "the variable regions can conveniently be derived from presently known sources using readily available hybridomas" (see column 6, last paragraph). Robinson et al teach that "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Huston et al teach "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Thus, the art recognized that there was a reasonable expectation of success that the nucleic acid sequence of the VH and VL of the art known RFB4 antibody could be established using techniques disclosed in the references used in the instant rejection. As taught by Ghetie the RFB4 antibody is a mouse IgG1 (see page 5876, right column) and as taught by Shen is produced by a hybridoma cell. One of ordinary skill in the art would

reasonably conclude that Ghetie et al's antibody also possesses the same VH and VL of SEQ ID NO:2 and 4, therefore, it appears that Ghetie et al's would have the same VH and VL sequences of SEQ ID NO:2 and 4. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody with the antibody of Ghetie et al, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 7/14/03 has been carefully considured but is deemed not to be persuasive. The response states That Orlandi et al teach the sequence in this region is determined by the primers the primers do not reflect the sequences of any particular VH or VL let alone the VH and VL sequences of RFB4 and the reference discusses the uncertainties in the sequence on page 3837 thus, different sequencing primers (as suggested by the examiner) would not solve the problem of obtaining the true sequence at the ends of the VH or VL, accordingly Orlandi with the other references would not reasonably be expected to lead to SEQ ID NO:2 and SEQ ID NO:4 as set forth in the claims. (see page 7 of response). In response to this argument, while Orlandi et al does indicate some variability in the sequence obtained,

the method did obtain the VH and VL for all of the five hybridomas for which it was applied. In addition, the new rejection adds references that clearly provide ample basis for a reasonable expectation of success to obtain SEQ ID NO:2 and SEQ ID NO:4 from the hybridoma or antibody of Shen et al and Ghettie et al. In addition, it would not require undue experimentation and one would have an expectation of success to obtain SEQ ID NO:2 and SEQ ID NO:4 because Shen teach the hybridoma and the using the methods cited in the references the hybridoma contains the VH and VL for the RFB4 antibody and thus the sequences of the DNA encoding SEQ ID NO:2 and 4 would be obtained.

The response further states "Applicants also cited Reiter et al (Nature Biotechnology 14:1239-1245) to support that the superior binding properties, i.e., RBF4dsFv immunoconjugates having the binding affinity that is essentially equivalent to the binding affinity of the unconjugated RFB4 IgG, can be predicted for a specific antibody" (see page 7 of response) and The examiner argues that Table 3 of Reiter clearly demonstrates that in almost every case the cytotoxicity of the dsFv is better than the scFv and Applicants note that the binding of the dsFv immunoconjugates is equivalent to the parent IgG in only a minority of the cases and cited Krietman et la for demonstrating that dsFV versions of an LL2 antibody had low activity and the superior binding properties and cytotoxicity of the claimed anti-CD22 immunoconjugates are unexpected and surprising (see page 7-8 of response).

In response to this argument, It is unclear if applicants are directing the examiner to the Reiter et al (Nature Biotechnology) or Reiter et al (Biochemistry) for

demonstration of dsFv immunoconjugates not being equivalent to the parent IgG. Reiter et al (Nature Biotech) teach 4 out of 8 dsFv-immunotoxins had improved binding affinity (see page 1243, left column). The Reiter et al (Biochemistry) clearly shows better cytotoxicity for the dsFV as compared to the scFv and better expression yields (see Table 1) and better stability (see Table 2) and teach "that dsFv's have at least the same binding properties as scFv's, and in some cases they may be better" (see abstract) and Reiter et al teach that scFv can retain the specificity and affinity of IgG (see page 5451). In addition, because the dsFv have superior characteristics over the scFv they would obviously be chosen over scFv and in addition Shen et al teach that the Fab'-RFB4 bound 1.2 to 3.5 times more stronger than other Fab' fragments and the potent cytotoxic activity of the RFB4-AS appears to derive from their superior binding affinity and the art recognizes the superiority of this antibody. With regard to the Krietman et al reference, this reference demonstrates only one instant where the dsFv had low activity, however, in all of Reiter et al (Biochemistry) and Kuan et al (Biochemistry) the dsFv were active and potent and as such one skill in the are would have a reasonable expectation of success in making the claimed immunoconjugate dsFv with the RFB4 antibody.

Conclusions

8. No Claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, PH.D
PRIMARY EXAMINER